AMERICAN VETERINARY MEDICAL ASSOCIATION
WASHINGTON D.C. OFFICE
1101 VERMONT AVENUE N.W., SUITE 710 • WASHINGTON, D.C. 20005-3521
PHONE 202-789-0007 • 800-321-1473 • FAX 202-842-4360

September 5, 1997

Docket Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive
Room 1-23
Rockville, MD 20857

Dear Sir or Madam:

We are responding to [Docket No. 97N-0217] Request for Comments on Development of Options to Encourage Animal Drug Approvals for Minor Species and for Minor Uses. These comments were developed by the American Veterinary Medical Association's Aquaculture & Seafood Advisory Committee (ASAC) and are intended to address the need for FDA-approved drugs for treatment of aquatic animals. The AVMA will also submit comments intended to address the need for approval of minor use/minor species drugs for use in terrestial animals.

At present only four drugs intended for aquatic species have been approved by the FDA. In spite of efforts to facilitate approvals of aquatic species drugs through the National Research Support Project No. 7 (NRSP-7) and the National Coordinator for Aquaculture New Animal Drug Applications, there have been no approvals of aquatic species drugs for the past several years. Although the United States is a world leader in production of terrestial species used for food, fiber, or companionship, the country is far behind in the production of aquatic species. We understand that the U.S. produces less than 3% of the world's output from aquaculture. The lack of availability of FDA-approved therapeutic agents for combating disease and improving reproductive efficiency appears to be one of the major reasons why the U.S. lags so far behind the rest of the world in aquaculture production. The U.S. imports seafood from around the world, including Southeast Asia where a number of antimicrobial products, not legally available in the U.S., are used for disease treatment and prevention. Florfenicol, for example, has been approved and in use in fish in Japan for a number of years. The product was first approved in the U.S. for use in cattle in 1996, after being in the FDA-CVM approval pipeline for over 15 years. The aquaculture drug approval process must become more streamlined and innovative before the aquaculture industry can be competitive on the world scene.

The June 23, 1997 Federal Register request for comments enumerated several possible regulatory and legislative measures that might facilitate minor species/minor use drug approvals. We suggest that all of the measures listed are worthy of consideration and implementation.

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Legislative changes that might be particularly important to future approvals of drugs for aquatic species would include: 1) tax incentives for drug sponsors that would allow deduction of a multiple of actual development and approval costs from federal taxes paid by the company; 2) extended marketing exclusivity or patent extension for the previously approved drug intended for use in a major species when a supplemental or additional approval for a minor use/minor species is obtained; 3) marketing of minor species/minor use drugs on a conditional basis as a means of developing the complete data package required for full approval; 4) third-party or non-agency fee-basis reviews of new animal drug applications based on FDA recognition of qualified third-party reviewers who are paid by the drug sponsor, and; 5) acceptance of approval data generated outside the U.S. when that data is generated under requirements similar to those in the U.S.

Administrative measures that would facilitate approval of drugs for aquatic species should include: 1) providing for approvals by means of the principles of the flexible/professional labeling concept, whereby sponsors might include minor species/minor use data on the product label from research generated by the sponsor with the understanding that a sponsor must show significant and continuous time-limited progress toward completing a supplemental approval for the minor species/minor use; 2) giving sponsors of new animal drugs for minor uses or minor species the opportunity to develop and validate their own good manufacturing practice requirements that may not be in the same lock-step process that is currently required; 3) providing exceptions to the individual approval requirements for each species of aquatic animals that would include reference to "crop grouping" to allow, for example, approval in one species of cold water fish to be applied to similar uses in other cold water species; 4) recognizing non-food stages of the aquatic food animal life cycle, such as eggs, fry, and fingerlings for which there is an "inherent withdrawal time" after treatment, and for broodstock that will never enter the human food supply, and; 5) recognize that a number of drug products approved for use in terrestial species are being marketed over-the-counter for use in non-food ornamental, tropical, or companion aquatic species and provide for a modified approval process based on animal safety data to allow for continued legal marketing of these products. Label extensions from drugs approved for food fish should be expanded to non-food species without the requirement of additional data.

There are several areas tangential to the approval process that must be addressed regarding drugs for use in aquatic species. **Extra-label use of reproductive hormones** in aquatic species is often necessary for the survival of an aquacultural enterprise. We understand that the Animal Medicinal Drug Use Clarification Act (AMDUCA) legislation did not legalize such extra label use by veterinarians. We believe that issuance of an FDA compliance policy guide that would permit the use of reproductive hormones under veterinary supervision or a legislative change to legalize such use is imperative. We understand that an import alert on reproductive hormones has been lifted. That being the case, there is concern that foreign-source products may be being imported into the U.S. and that their use may be taking place without appropriate involvement by veterinarians. A more satisfactory regulatory solution to the reproductive hormone use issue may be to grant state veterinarians authority for importation of reproductive hormones approved in other countries when FDA-approved products are not available.

The administration of drugs to aquatic species is often problematic in that incorporation into feed may often be the most effective route of administration. Extra-label use of drugs added to feeds is prohibited by AMDUCA, even if such extra-label use is engaged in by veterinarians. The Veterinary Feed Directive section of the Animal Drug Availability Act (ADAA) may provide some administrative leeway, wherein a compliance policy guide could be generated to allow limited veterinarian-

supervised extra-label use of drugs in fish feed to deal with disease outbreaks in aquatic species when an approved use or dosage is either not available or clinically ineffective.

Another area that we believe must be addressed by FDA-CVM is the **cost of approval of minor species/minor use drugs** compared to the potential market for those drugs. Reviewers should be encouraged to consider the added cost of generation of additional information as it relates to the safe and effective use of the product. Each step in the approval process should include consideration as to whether the particular requirement needs to be met to the last iota, and whether such exacting requirements will actually contribute to the drug's effectiveness, its human or animal safety, or whether it will simply add to the final cost of the approved product.

We urge the FDA-CVM to consider implementation of our proposals in a meaningful and realistic time frame. Thank you for the opportunity to comment on this important issue.

Sincerely,

Bruce W. Little

Bruce W. Little, Executive Vice President, AVMA

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